REMARKS

Claims 1-37 constitute the pending claims in the present application. Claims 38-67 have been added. The subject matter of these claims is fully supported by the specification as filed. Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action.

1. As requested, Applicants have attached for submission a signed declaration by the inventor.

2. As requested, Applicants have attached for submission corrected drawings for Figure 3.

3. The abstract of the disclosure is objected to because it "is insufficiently detailed as to the identity of the active agents which are used." Applicants have amended the abstract to provide added details pertaining to the active agents of the present application. Applicants respectfully request reconsideration and removal of the aforementioned objection in light of the amendment.

4. The claim for priority inserted by the preliminary amendment filed July 28, 2000, is objected to as not indicate what type of priority is being claimed. Applicants assert that the instant application is a continuation of PCT Application US99/02294, filed on 02/02/99, which in turn claims priority to US Application 60/073,409, filed on 02/02/98. Applicants have included new Declaration with this Response, to support this claim. Thus, Applicants assert that there is proper co-pendency between the two applications. Applicants respectfully request reconsideration of the Examiner's objection.

5. The disclosure is objected to because of typographical informalities. Applicants have made the requested corrections and any repetitions of the same misspelling. Applicants have corrected misspelling at page 9, line 6 from "organis" to "organics". Applicants have corrected misspelling at page 18, line 10, from "lik" to "like". Applicants respectfully request reconsideration of this objection in view of the amendments.

6. Claims 15-28 and 31-37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Accordingly,

a. Applicants have amended claim 15 to state "a Cα carbon" instead of "the Cα carbon". Applicants submit that this amendment does not narrow the scope of the claim.

b. Applicants have removed the phrases reciting "such as" from claim 15. Applicants submit that this amendment does not narrow the scope of the claim.

c. Applicants have replaced reference to the variable "X" in claim 15 with the variable "Z" as would be understood by one with ordinary skill in the art.. Applicants submit that this amendment does not narrow the scope of the claim.

d. Applicants have made changes to structures in claims 16 and 28 wherein a single bonded monovalent oxygen has been changed to a double bonded divalent oxygen as would be understood by one with ordinary skill in the art.. Applicants assert that one of ordinary skill in the art would have recognized this error, and the obvious correction. Thus, Applicants submit that this change does not narrow the scope of the claim.

e. Applicants have edited claims 16, 28 and 31 to remove the phrases "such as" and "including", and "such as pinacol or the like". Applicants submit that this amendment does not narrow the scope of the claims.

f. As to the This rejection of claims 20 and 21 because the "correspondence is not clear between the [phrase] small hydrophobic groups of claims 20 and 21 and the substituents recited in the definitions of R_2 and R_3 in claim 15", Applicants respectfully traverse the rejection. Applicants point out that the phrase "small hydrophobic groups" has been used in the specification numerous times to refer to lower alkyls or halogens (see page

11 lines 20-21, 23-25; page 16 lines 1-2, 6-8). The term "lower alkyls" is also defined in the specification. Thus Applicants maintain that there is a sufficient correspondence for the dependence of claims 20 and 21 on claim 15.

g. Applicants have made a change in the structure represented in the general formula to clarify that R_1 is attached to the amino terminus as would be understood by one with ordinary skill in the art.. Applicants assert that one of ordinary skill in the art would have recognized this error, and the obvious correction. Thus, Applicants submit that this change does not narrow the scope of the claim.

h. Applicants have amended claim 28 to state, "active site residue of the targeted protease selected from" instead of "active site residue of the targeted protease, for example". Applicants submit that this amendment does not narrow the scope of the claim.

i. Applicants have amended claim 31 by removing references to R_5 and R_{61} and adding the variables R_7 and R_{61} as would be understood by one with ordinary skill in the art.. Applicants assert that one of ordinary skill in the art would have recognized this error, and the obvious correction. Thus, Applicants submit that this change does not narrow the scope of the claim.

j. Applicants have amended claim 31 by replacing the phrase "represents small hydrophobic groups, preferably lower alkyls, and more preferably methyl" with the phrase "represents lower alkyl or halogen". Applicants submit that this change does not narrow the scope of the claim.

k. Applicants have amended claim 37 by replacing the phrase "including boronyl inhibitor of peptidomimetic of a peptide selected from the group consisting Pro-Pro, Ala-Pro, and (D)-Ala-(L)-Ala" with the phrase "comprising a peptidomimetic boronyl inhibitor wherein the peptide to be mimicked is selected from Pro-Pro, Ala-Pro, and (D)-Ala-(L)-Ala." Applicants submit that this change does not narrow the scope of the claim.

Applicants respectfully request reconsideration of this rejection in view of the amendments.

7. Applicants have corrected the informalities (cited on page 6, section 8 of the Office Action) in claims 4-7, 15-28, and 30-36 which the Examiner had found objectionable. Applicants assert that one of ordinary skill in the art would have recognized these errors, and the obvious correction. Thus, Applicants submit that the changes do not narrow the scope of the claims. Applicants respectfully request reconsideration of these objections in view of the amendments.

8. Claims 22, 24-26, and 28 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicants submit that the source of the objection is, in part, due to the renumbering of the claims. Applicants have amended claims 22, 24-26 to place the claims in proper dependent form, by replacing references to "claim 16" in each of the claims to "claim 15" as would be understood by one with ordinary skill in the art.. Applicants assert that one of ordinary skill in the art would have recognized these errors, and the obvious correction. Thus, Applicants submit that these change do not narrow the scope of the claim. Applicants have also changed the dependency of claim 28 from claim 16 to claim 1, 2, 3, 4 or 15. Applicants respectfully request reconsideration of these objections in view of the amendments.

9. Applicants have corrected informalities cited in the Office Action in claims 15,16 and 28. Applicants assert that one of ordinary skill in the art would have recognized these errors, and the obvious correction. Thus, Applicants submit that these changes do not narrow the scope of the claims.

10. Claims 1, 3, 5-10, 12, 13, and 29 are rejected under 35 U.S.C 102(b) as being anticipated by the Deacon *et al.* article. Applicants respectfully traverse this rejection. Applicants assert that the instant application is a continuation of the PCT Application US99/02294 filed 02/02/99, which in turn claims priority to the US Application 60/073,409, filed on 02/02/98. Deacon et al. was published in 05/98. Applicants assert that the relationship between the instant application and 60/073,409 falls within the condition set forth in MPEP 201.11(a) for receiving the benefit of an earlier filing date: namely, the claimed invention is disclosed in 60/073,409, and sufficiently to complies with the requirements of the first paragraph of 35 U.S.C. 112. Applicants respectfully request reconsideration of this rejection in view of the aforementioned argument.

11. Claims 1, 3, 5-16, 20, 21, 25, and 29 are rejected under 35 U.S.C 102(b) as being anticipated by the WO Patent Application 95/15309 (hereafter referred to as "'309 application"). Applicants respectfully traverse the This rejection. While the '309 application claims DPIV inhibitors, it does not disclose every element of the presently claimed subject matter of the instant application because it does not teach or suggest that DPIV inhibitors can be used to modulate GLP-1 metabolism. For instance, suggestions for modulating GLP-1 metabolism are absent in the list of contemplated uses in the '309 application. (See '309 app., page 3) In contrast, the instant claims are directed towards methods for modulating GLP-1 metabolism. The '309 application does not teach, suggest or anticipate a method for using DPIV inhibitors for modulating GLP-1 metabolism. The fact that GLP-1 metabolism may have been modified to the same extent in the experiments described in the '309 application is not relevant because, in inherency anticipation of method claims, if a claimed method comprises steps identical to those of a method practiced in the prior art, and the same result would have been achieved in the prior art method, the accidental or unwitting achievement of that result cannot constitute anticipation. *In re Marshall*, 578 F.2d 301, 198 USPQ 344 (CCPA 1978) Any modulation of GLP-1 metabolism in the experiments described in the '309 application would have been an unrecognized accident, and thus cannot constitute inherent anticipation of the instant claims. Therefore, Applicants respectfully request reconsideration of the inherency rejection in view of the aforementioned argument.

With respect to claim 14, Applicants have amended the claim to state "administered orally" instead of "orally active." Applicants have further amended claim 36 in a similar fashion. Applicants submit that this change does not narrow the scope of the claim.

12. Claims 2, 11, 14-16, 20, 21 and 25 are rejected under 35 U.S.C. 103(a) as being obvious over the Deacon *et al.* article as applied against claims 1, 3, 5-10, 12, 13, and 29 and further in view of the '309 application. Applicants respectfully traverse this rejection because Deacon et al. does not qualify as prior art for reasons stated above. Consequently, the Deacon article is not available art for an objection under 35 U.S.C. 103. The '309 Application alone does not disclose all the elements of the pending invention for reasons set forth above. Applicants respectfully request reconsideration of this rejection.

13. Claims 1-3, 5-24, 26, 27, and 29-37 are rejected under 35 U.S.C. 102(b) as being anticipated by the WO Patent Application 93/08259 (hereafter referred to as the '259

Application). Applicants respectfully traverse this rejection. While the '259 application makes composition of matter claims of DPIV inhibitors, it does not disclose every material element of the claimed subject matter of the instant application because it does not teach or suggest that DPIV inhibitors can be used to modulate GLP-1 metabolism. In contrast, the instant claims are directed towards methods for modulating GLP-1 metabolism. The '259 application does not teach, suggest or anticipate a method for using DPIV inhibitors for modulating GLP-1 metabolism. The fact that GLP-1 metabolism may have been modified to the same extent in the experiments described in the '259 application is not relevant because, in inherency anticipation of method claims, if a claimed method comprises steps identical to those of a method practiced in the prior art, and the same result would have been achieved in the prior art method, the accidental or unwitting achievement of that result cannot constitute anticipation. *In re Marshall*, 578 F.2d 301, 198 USPQ 344 (CCPA 1978) Any modulation of GLP-1 metabolism in the experiments described in the '259 application would have been an unrecognized accident, and thus cannot constitute inherent anticipation of the instant claims. Therefore, Applicants respectfully request reconsideration of this rejection.

14. Claims 2, 11, 14-16, 20, 21 and 25 are rejected under 35 U.S.C. 103(a) as being obvious over the Deacon *et al.*, further in view of the '259 application. Applicants respectfully traverse this rejection because Deacon et al. does not qualify as prior art for reasons stated above. The '259 Application alone does not teach all the elements of the present claims. Accordingly, Applicants respectfully request reconsideration of this rejection.

15. Claim 4 is rejected under 35 U.S.C. 103(a) as being obvious over Deacon et al., and further in view of Efendic *et al.* Applicants respectfully traverse this rejection. Applicants assert that Deacon et al. does not qualify as prior art for reasons stated above. In the absence of the Deacon article, Efendic et al. does not teach or suggest all the elements of the present claims. Namely, it does not teach the element of administering a DPIV inhibitor to modifying GLP-1 metabolism. Thus, there would be no motivation for one of ordinary skill in the art at the time of filing to use of DPIV inhibitors for treatment of Type II diabetes. Therefore, Applicants assert that a 35 U.S.C 103(a) obviousness rejection cannot be sustained. Applicants respectfully request reconsideration of this rejection.

16. Claims 1-3, 5-24, 26, 27, and 29-37 are rejected under 35 U.S.C. 102(b) as being anticipated by the WO Patent Application 98/25644 (hereafter referred to as the '644 Application). Applicants respectfully traverse this rejection. The International

publication date of the '644 application is 06/18/98. The instant application claims priority to the US Application 60/073,409, filed on 02/02/98. Thus, the '644 application is unavailable as prior art under 35 U.S.C. 102(b), thereby rendering this rejection moot. Applicants respectfully request reconsideration of this rejection.

17. Claims 1-17, 20, 21 and 29 are rejected under 35 U.S.C. 102(a) and (e) as being anticipated by Villhauer's US Patent 6,011,155 (hereafter referred to as the '155 patent). Applicants respectfully traverse this rejection. Applicants have added a K_i limitation of 1 nM or less to claims 1-4 and 29. Thus, with respect to claim 1, Applicants assert that the '155 patent does not teach or suggest a method for modifying metabolism of glucagon-like peptide 1 (GLP-1), comprising administering to an animal a composition including one or more inhibitors of a dipeptidylpeptidase which inactivates GLP-1, which inhibitor(s) inhibit(s) the dipeptidylpeptidase proteolysis of GLP-1 at a K_i of 1 nM or less. As such, the '155 patent does not anticipate claim 1 of the claimed invention because it does not disclose all the limitation of the instant claim, namely a limitation having a K_i of 1 nM less.

The Office action stated,

> "[W]ith respect to instant claims 2 and 8-11, in view of the similarity in structure and function between the DPIV inhibitor or Villhauer and Applicant's claimed DPIV inhibitor, the EC_{50}'s and K_i for the DPIV inhibitors of Villhauer will inherently be the same as is recited in instant claims 2 and 8-11."

Applicants respectfully disagree. The '155 patent does not provide K_i or EC_{50} limitation for any of the claims or in the specification. The '155 patent only discloses IC_{50} values of inhibitors against human and rat plasma DPIV, as well as against human colonic carcinoma cell extracts. According to the Cheng-Prusoff equation (Biochem. Pharmacol. 22:3099-3108, 1973, included herewith as Exhibit A), K_{id} values will always be less than or equal to IC_{50} values. The lowest IC_{50} cited in the '155 patent is a value of 3 nM for Compound Ex.49 against rat plasma DPP-IV. ('155 patent, column 9, line 33) Since the K_i limitation of the instant claims 1-4 is 1 nM, Applicants assert that the Ki values for the DPIV inhibitors of Villhauer cannot inherently meet the limitation. Claims dependent on claims 1-4 are thus novel over Villhauer for the reasons stated above. Accordingly, Applicants respectfully request reconsideration of this rejection.

Claim 29 because "the same active agents are being administered to the same animals according to the same method steps, inherently peptide hormone metabolism will be modified to

the same extent in the method of Villhauer as is claimed by Applicants." Applicants have amended the claim to contain a K_i limitation of 1 nM or less to the DPIV inhibitors cited in claim 29. As stated above, none of the compounds in the '155 patent have been shown to have K_is of 1 nM or less. Applicants submit that the method of modifying, in an animal, metabolism of peptide hormone by administering one or more DPIV inhibitors with K_is 1 nM or less is not is not taught in the '155 patent. Therefore, Applicants submit that the '155 patent does not anticipate claim 29.

In summary, Applicants assert the DPIV inhibitors of the '155 patent would not have Kis lower than 1 nM, and thus the methods disclosed in the '155 patent do not anticipate the instant method claims. Accordingly, Applicants respectfully urge reconsideration of this rejection.

New Claims:

Additionally, Applicants assert that the new claims are novel and unobvious because cited references do not teach or suggest the use of DPIV inhibitors to modify glucose metabolism in *glucose intolerant* animal models. For example, the '155 patent only tested compounds in male Sprague-Dawley rats. These rats are glucose tolerant. ('155 patent, column 9, line 66) In contrast, the instant application not only demonstrates the efficacy of the instant DPIV inhibitors in glucose tolerant rat models, but it also demonstrates efficacy of the instant DPIV inhibitors in GLP-1 gene "knock out" mice that are in fact glucose intolerant. (p.51, Example 5) It is apparent that glucose tolerant rats have endocrine systems that are substantially different from rats that are glucose intolerant. Given the complexities of the endocrine system, one of ordinary skill in the art could not reasonably expect that compounds that increase glucose tolerance in *glucose tolerant* models would also increase glucose tolerance in *glucose intolerant models*. As such the '155 application teaching of increasing glucose tolerance by administering a DPIV inhibitor is only limited to animals which are already glucose tolerant. The teaching cannot be extended to glucose intolerant animals because the '155 patent does not provide one of ordinary skill in the art with a reasonable expectation that DPIV inhibitors are effective in glucose intolerant animals. It is an established principle that what may be obvious to try does not make an invention obvious. Instead, the instant application first demonstrated that DPIV inhibitors are effective for increasing glucose tolerance in glucose intolerant animals. Accordingly, Applicants submit the cited art neither anticipates nor renders obvious the subject matter of claim 38-67.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945.**

Respectfully Submitted,

Date: November 30, 2001

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In the specification:

1. On page 9, line 6-8, please replace the existing paragraph with one cited below.

In other embodiments, the inhibitor is a non-peptidyl compound, e.g., which can be identified by such drug screening assays as described herein. These inhibitors can be, merely to illustrate, synthetic organics, natural products, nucleic acids or carbohydrates.

2. On page 18, line 10, please replace the existing sentence with one cited below.

In preferred embodiments, R_{61} and R_{62}, independently, represent low alkyls, such as methyl, ethyl, propyl, isopropyl, tert-butyl or the like;

The specification presented above incorporates changes as indicated by the marked-up version below.

1. These inhibitors can be, merely to illustrate, synthetic ~~organis~~ organics, natural products, nucleic acids or carbohydrates.

2. In preferred embodiments, R_{61} and R_{62}, independently, represent low alkyls, such as methyl, ethyl, propyl, isopropyl, tert-butyl or the ~~lik.~~ like;

In the abstract:

On page 65, lines 1-7, please replace the abstract with the one presented below.

The present invention provides methods and compositions for modification and regulation of glucose and lipid metabolism, generally to reduce insulin resistance, hyperglycemia, hyperinsulinemia, obesity, hyperlipidemia, hyperlipoproteinemia (such as chylomicrons, VLDL and LDL), and to regulate body fat and more generally lipid stores, and, more generally, for the improvement of metabolism disorders, especially those associated with diabetes, obesity and/or atherosclerosis. The compositions of the present invention include dipeptidylpeptidase inhibitors, which are able to inhibit the proteolysis of GLP-1 and accordingly increase the plasma half-life of that hormone. The subject inhibitors may be peptidyl, peptidomimetic (e.g. boronyl peptidomimetics), or non-peptidyl nitrogen containing heterocycles.

The abstract presented above incorporates changes as indicated by the marked-up version below.

The present invention provides methods and compositions for modification and regulation of glucose and lipid metabolism, generally to reduce insulin resistance, hyperglycemia, hyperinsulinemia, obesity, hyperlipidemia, hyperlipoproteinemia (such as chylomicrons, VLDL and LDL), and to regulate body fat and more generally lipid stores, and, more generally, for the improvement of metabolism disorders, especially those associated with diabetes, obesity and/or atherosclerosis. The compositions of the present invention include dipeptidylpeptidase inhibitors, which are able to inhibit the proteolysis of GLP-1 and accordingly increase the plasma half-life of that hormone. The subject inhibitors may be peptidyl, peptidomimetic (e.g. boronyl peptidomimetics), or non peptidyl nitrogen containing heterocycles.

Y_1 and Y_2 can independently or together be OH or an alkoxyl, or taken together Y_1 and Y_2 are connected via a ring having from 5 to 8 atoms in the ring structure which is hydrolyzed to hydroxy groups under physiological conditions;

R_{50} represents O or S;

R_{51} represents N_3, SH, NH_2, NO_2 or OR'_7;

B6 cont.

R_{52} represents hydrogen, a lower alkyl, an amine, OR'_7, or a pharmaceutically acceptable salt, or R_{51} and R_{52} taken together with the phosphorous atom to which they are attached complete a heterocyclic ring having from 5 to 8 atoms in the ring structure;

X_1 represents a halogen;

X_2 and X_3, independently for each occurrence, represent a hydrogen or a halogen;

m is zero or an integer in the range of 1 to 8; and

n is an integer in the range of 1 to 8.

The claims presented above incorporate changes as indicated by the marked-up versions below.

1. (Amended) A method for modifying, in an animal, metabolism of glucagon-like peptide 1 (GLP-1), comprising administering to the animal a composition including one or more inhibitors of a dipeptidylpeptidase which inactivates GLP-1, which inhibitor(s) are ~~administered in an amount sufficient to~~ inhibit(s) the dipeptidylpeptidase proteolysis of GLP-1 having a Ki of 1 nM or less.

2. A method for modifying glucose metabolism of an animal, comprising administering to the animal a composition including one or more protease inhibitors which inhibit DPIV-mediated proteolysis ~~with~~ having a Ki of 1 nM or less.

3. (Amended) A method for modifying glucose metabolism of an animal, comprising administering to the animal a composition including one or more protease inhibitors which

inhibit the proteolysis of glucagon-like peptide 1 (GLP-1) having a K_i of 1 nM or less, and ~~accordingly increase the plasma half-life of GLP-1~~.

4. (Amended) A method for treating Type II diabetes, comprising administering to an animal a composition including one or more inhibitors of dipeptidylpeptidase IV (DPIV) having a K_i of 1 nM or less.

5. (Amended) The method of claim 1, wherein the dipeptidylpeptidase is DPIV.

6. (Amended) The method of claim 2 or 3, wherein the protease inhibitor is an inhibitor of DPIV.

7. (Amended) The method of claim 2 or 3, wherein administering the inhibitor reduces one or more of insulin resistance, glucose intolerance, hyperglycemia, hyperinsulinemia, obesity, hyperlipidemia, or hyperlipoproteinemia.

8. (Amended) The method of claim 1, 2, 3 or 4, wherein the inhibitor has an EC_{50} for modification of glucose metabolism which is at least one order of magnitude less than its EC_{50} for immunosuppression.

9. (Amended) The method of claim 1, 2, 3 or 4, wherein the inhibitor has an EC_{50} for inhibition of glucose tolerance in the nanomolar or less range.

10. (Amended) The method of claim 1, 2, 3 or 4, wherein the inhibitor has an EC_{50} for immunosuppression in the ~~M~~ μM or greater range.

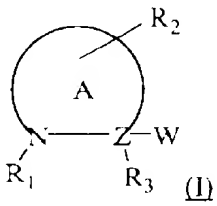
11. (Amended) The method of claim 1, 2, 3, or 4, ~~5 or 6,~~ wherein the inhibitor has a K_i for DPIV inhibition of ~~1.0~~0.5 ~~nm~~nM or less.

12. (Amended) The method of claim 1, 2, 3 or 4, wherein the inhibitor is peptidomimetic of a peptide selected from the group consisting Pro-Pro, Ala-Pro, and (D)-Ala-(L)-Ala.

13. (Amended) The method of claim 1, 2, 3 or 4, wherein the inhibitor has a molecular ~~weights~~weight less than 7500 amu.

14. (Amended) The method of claim 1, 2, 3 or 4, wherein the inhibitor is _administered_orally ~~active~~.

15 (Amended) The method of claim 1, 2, 3 or 4, wherein the inhibitor is represented by the general ~~formula~~Formula I;



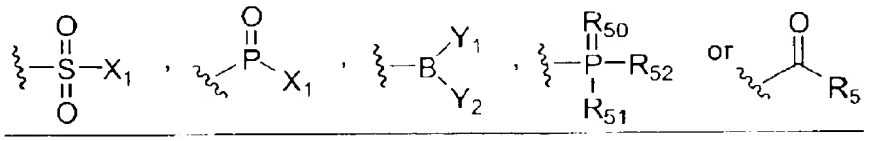
(I)

wherein,

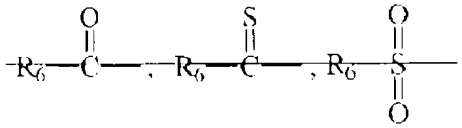
A represents a 4-8 membered heterocycle including ~~the~~ a N and ~~the~~ a C—α carbon;

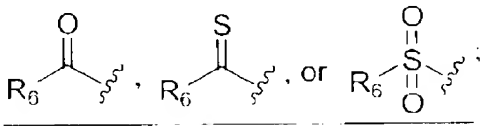
Z represents C or N;

W represents ~~a functional group which reacts with an active site residue of the targeted~~ protease-CN, -CH NR$_{5}$,



R_1 represents a C-terminally linked amino acid residue or amino acid analog, or a C- terminally linked peptide or peptide analog, or an amino-protecting group, or





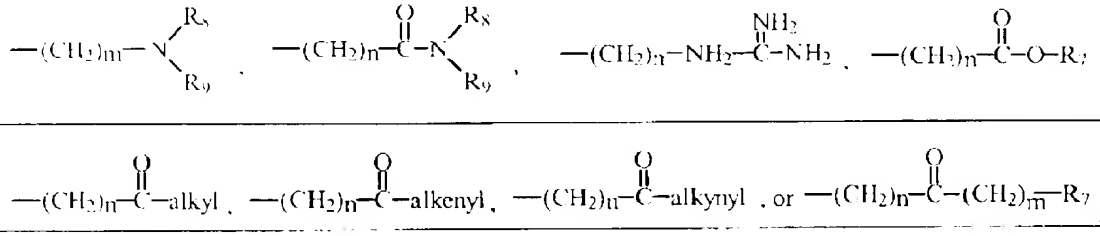
R_2 is absent or represents one or more substitutions to the ring A, each of which can independently be a halogen, a lower alkyl, a lower alkenyl, a lower alkynyl, a carbonyl ~~(such as a carboxyl, an ester, a formate, or a ketone)~~, a thiocarbonyl ~~(such as a thioester, a thioacetate, or a thioformate)~~, an amino, an acylamino, an amido, a cyano, a nitro, an azido, a sulfate, a sulfonate, a sulfonamido, - $(CH_2)_m$-R_7, -$(CH_2)_m$-OH, -$(CH_2)_m$-O-lower alkyl, -$(CH_2)_m$-O-lower alkenyl, -$(CH_2)_n$-O-$(CH_2)_m$-R_7, - $(CH_2)_m$-SH, -$(CH_2)_m$-S-lower alkyl, -$(CH_2)_m$-S-lower alkenyl, or -$(CH_2)_n$-S-$(CH_2)_m$-R_7;

if ~~X~~Z is N, then R_3 represents a hydrogen.;

if ~~X~~Z is C, then R_3 represents a hydrogen or a halogen, a lower alkyl, a lower alkenyl, a lower alkynyl, a carbonyl ~~(such as a carboxyl, an ester, a formate, or a ketone)~~, a thiocarbonyl ~~(such as a thioester, a thioacetate, or a thioformate)~~, an amino, an acylamino, an amido, a cyano, a nitro, an azido, a sulfate, a sulfonate, a sulfonamido, - $(CH_2)_m$-R_7, -$(CH_2)_m$-OH, -$(CH_2)_m$-O-lower alkyl, -$(CH_2)_m$-O-lower alkenyl, -$(CH_2)_n$-O-$(CH_2)_m$-R_7, - $(CH_2)_m$-SH, -$(CH_2)_m$-S-lower alkyl, -$(CH_2)_m$-S-lower alkenyl, or - $(CH_2)_n$-S-$(CH_2)_m$-R_7;

R_5 represents a hydrogen, an alkyl, an alkenyl, an alkynyl, -$C(X_1)(X_2)X_3$, -$(CH_2)_m$-R_7, -$(CH_2)_n$-OH, -$(CH_2)_n$-O-alkyl, -$(CH_2)_n$-O-alkenyl, -$(CH_2)_n$-O-alkynyl, -$(CH_2)_n$-O-$(CH_2)_m$-R_7, -$(CH_2)_n$-SH, -$(CH_2)_n$-S-alkyl, -$(CH_2)_n$-S-alkenyl, -$(CH_2)_n$-S-alkynyl, -$(CH_2)_n$-S-$(CH_2)_m$-R_7, -C(O)C(O)NH_2, or -C(O)C(O)OR'$_7$;

R_6 represents a hydrogen, a halogen, ~~a~~an alkyl, an alkenyl, an alkynyl, an aryl, -$(CH_2)_m$-R_7, -$(CH_2)_m$-OH, -$(CH_2)_m$-O-alkyl, -$(CH_2)_m$-O-alkenyl, -$(CH_2)_m$-O-alkynyl, -$(CH_2)_m$-O-$(CH_2)_m$-R_7, -$(CH_2)_m$-SH, -$(CH_2)_m$-S-alkyl, -$(CH_2)_m$-S-alkenyl, -$(CH_2)_m$-S-alkynyl, -$(CH_2)_m$-S-$(CH_2)_m$-R_7,



R$_7$ represents, for each occurrence, a substituted or unsubstituted aryl, aralkyl, cycloalkyl, cycloalkenyl, or ~~heterocycle~~ heterocyclyl;

R'$_7$ represents, for each occurrence, hydrogen, or a substituted or unsubstituted alkyl, alkenyl, aryl, aralkyl, cycloalkyl, cycloalkenyl, or heterocyclyl;

R$_8$ and R$_9$ each independently represent hydrogen, alkyl, alkenyl, -$(CH_2)_m$-R_7, -C(=O)-alkyl, -C(=O)-alkenyl, -C(=O)-alkynyl, or -C(=O)-$(CH_2)_m$-R_7,
or R$_8$ and R$_9$ taken together with the N atom to which they are attached complete a heterocyclic ring having from 4 to 8 atoms in the ring structure;

R_{50} represents O or S;

R_{51} represents N_3, SH, NH_2, NO_2 or OR'$_7$;

R_{52} represents hydrogen, a lower alkyl, an amine, OR'$_7$, or a pharmaceutically acceptable salt, or R_{51} and R_{52} taken together with the phosphorous atom to which they are attached complete a heterocyclic ring having from 5 to 8 atoms in the ring structure;

X_1 represents a hydrogen or a halogen, or a hydroxyl;

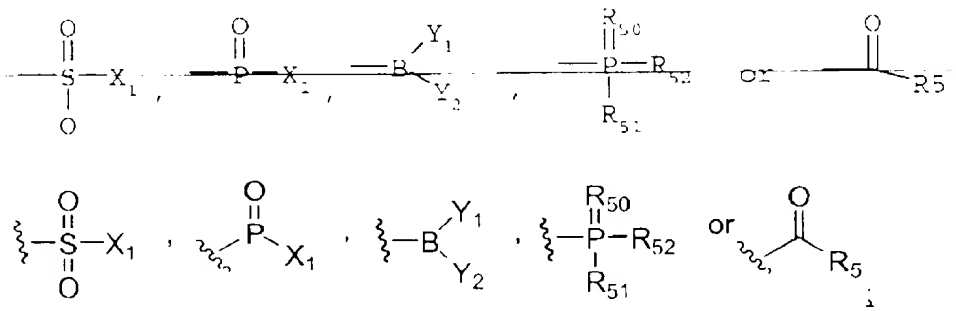
X_2 and X_3 each represent a hydrogen or a halogen;

m is zero or an integer in the range of 1 to 8; and

n is an integer in the range of 1 to 8.

16. (Amended) The method of claim 15, wherein,

W represents -CN, -CH=NR_5,



R_5 represents ~~Ha~~ hydrogen, an alkyl, an alkenyl, an alkynyl, $-C(X_1)(X_2)X_3$, $-(CH_2)_m-R_7$, $-(CH_2)_n-OH$, $-(CH_2)_n-O-alkyl$, $-(CH_2)_n-O-alkenyl$, $-(CH_2)_n-O-alkynyl$, $-(CH_2)_n-O-(CH_2)_m-R_7$, $-(CH_2)_n-SH$, $-(CH_2)_n-S-alkyl$, $-(CH_2)_n-S-alkenyl$, $-(CH_2)_n-S-alkynyl$, $-(CH_2)_n-S-(CH_2)_m-R_7$, $-C(O)C(O)NH_2$, or $-C(O)C(O)OR'_7$;

R_7 represents, for each occurrence, a substituted or unsubstituted aryl, aralkyl, cycloalkyl, cycloalkenyl or heterocyclyl;

R'_7 represents, for each occurrence, hydrogen, or a substituted or unsubstituted alkyl, alkenyl, aryl, aralkyl, cycloalkyl, cycloalkenyl, or ~~heterocycle~~heterocyclyl; ~~and~~

Y_1 and Y_2 can independently or together be OH, ~~or a group capable of being hydrolyzed to a hydroxyl group, including cyclic derivatives where,~~ or an alkoxyl, or, taken together, Y_1 and Y_2 are connected via a ring having from 5 to 8 atoms in the ring structure ~~(such as pinacol or the like),~~ which is hydrolyzed to hydroxy groups under physiological conditions;

R_{50} represents O or S;

R_{51} represents N_3, SH_2, NH_2, NO_2 or OR'_7;

R_{52} represents hydrogen, a lower alkyl, an amine, OR'_7, or a pharmaceutically acceptable salt, or R_{51} and R_{52} taken together with the phosphorous atom to which they are attached complete a heterocyclic ring having from 5 to 8 atoms in the ring structure;

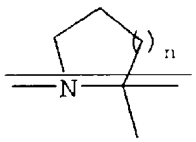
X_1 represents a hydrogen or a halogen, or a hydroxyl;

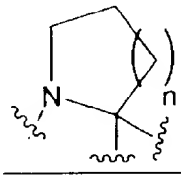
X_2 and X_3 each independently represent a hydrogen or a halogen;

m is zero or an integer in the range of 1 to 8; and

n is an integer in the range of 1 to 8.

~~18.~~ 17. (Amended)The method of claim ~~16~~15, wherein the ring A is represented by the formula

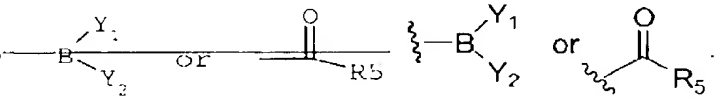




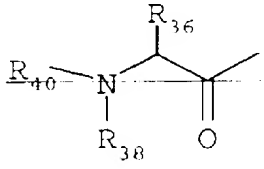
wherein,

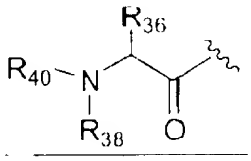
n is an integer of 1 or 2.

~~19.~~ 18. (Amended) The method of claim ~~16~~15, wherein W

represents  .

~~20.~~ 19. (Amended) The method of claim ~~16~~15, wherein R_1 represents





~~wherein~~

R_{36} is<u>represents</u> a small hydrophobic group and R_{38} is hydrogen, or, R_{36} and R_{38} together form a 4-7 membered heterocycle including ~~the~~ <u>a</u> N and ~~the~~ <u>a</u> <u>C—α</u> carbon; and

R_{40} represents a C-terminally linked amino acid residue or amino acid analog, or a C-terminally linked peptide or peptide analog, or an amino-protecting group.

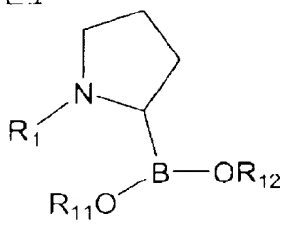
~~21.~~ <u>20.</u> (Amended) The method of claim ~~16~~<u>15</u>, wherein R_2 is absent, or represents a small hydrophobic group.

~~22.~~ <u>21.</u> (Amended) The method of claim ~~16~~<u>15</u>, wherein R_3 is a hydrogen, or a small hydrophobic group.

~~23.~~ <u>22.</u> (Amended) The method of claim ~~16,~~<u>15</u>, wherein R_5 is a hydrogen, or a ~~halogentated~~<u>halogenated</u> lower alkyl.

~~24.~~ <u>23.</u> (Amended) The method of claim ~~16~~ <u>15</u>, wherein X_1 is a fluorine, and X_2 and X_3, if halogens, are fluorine.

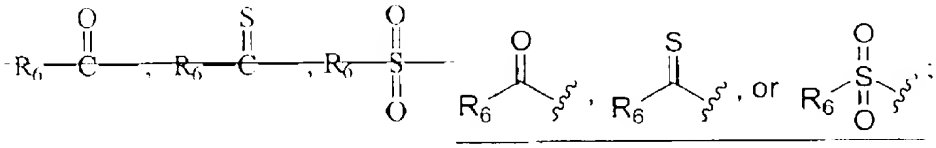
~~25.~~ <u>24.</u> (Amended) The method of claim ~~16~~<u>15</u>, wherein the inhibitor is represented by the general ~~formula~~<u>Formula (II)</u>:



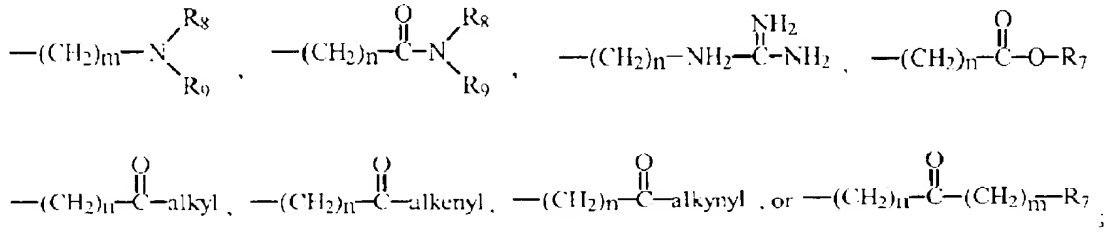
<u>(II)</u>

wherein ,

R_1 represents a C terminally linked amino acid residue or amino acid analog, or a C-terminally linked peptide or peptide analog, or



R_6 represents a hydrogen, a halogen, ~~a~~an alkyl, ~~a~~an alkenyl, ~~a~~an alkynyl, an aryl, $-(CH_2)_m-R_7$, $-(CH_2)_m-OH$, $-(CH_2)_m-O-alkyl$, $-(CH_2)_m-O-alkenyl$, $-(CH_2)_m-O-alkynyl$, $-(CH_2)_m-O-(CH_2)_m-R_7$, $-(CH_2)_m-SH$, $-(CH_2)_m-S-alkyl$, $-(CH_2)_m-S-alkenyl$, $-(CH_2)_m-S-alkynyl$, $-(CH_2)_m-S-(CH_2)_m-R_7$,



R_7 represents an aryl, a cycloalkyl, a cycloalkenyl, or a heterocycle;

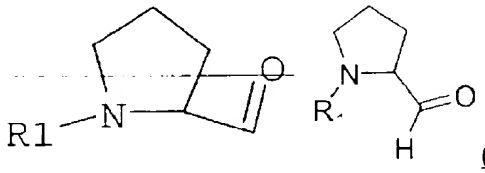
R_8 and R_9 each independently represent hydrogen, alkyl, alkenyl, $-(CH_2)_m-R_7$, -C(=O)-alkyl, -C(=O)-alkenyl, -C(=O)-alkynyl, or -C(=O)-$(CH_2)_m-R_7$,
or R_8 and R_9 taken together with the N atom to which they are attached complete a heterocyclic ring having from 4 to 8 atoms in the ring structure;

R_{11} and R_{12} each independently represent hydrogen, ~~a~~an alkyl, or a pharmaceutically acceptable salt, or R_{11} and R_{12} taken together with the O-B-O atoms to which they are attached complete a heterocyclic ring having from 5 to 8 atoms in the ring structure;

m is zero or an integer in the range of 1 to 8; and

n is an integer in the range of 1 to 8.

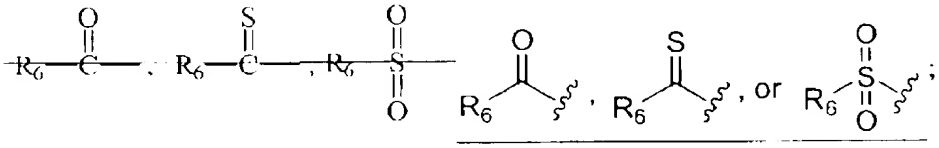
~~26.~~ 25. (Amended) The method of claim ~~16~~15, wherein the inhibitor is represented by the general ~~formula~~Formula III,



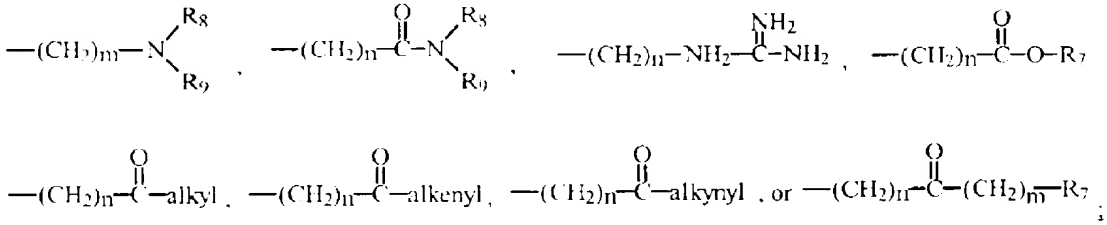
(III)

wherein,

R_1 represents a C-terminally linked amino acid residue or amino acid analog, or a C-terminally linked peptide or peptide analog, ~~or~~



R_6 represents a hydrogen, a halogen, ~~a~~an alkyl, ~~a~~an alkenyl, ~~a~~an alkynyl, an aryl, $-(CH_2)_m-R_7$, $-(CH_2)_m-OH$, $-(CH_2)_m-O$-alkyl, $-(CH_2)_m-O$-alkenyl, $-(CH_2)_m-O$-alkynyl, $-(CH_2)_m-O-(CH_2)_m-R_7$, $-(CH_2)_m-SH$, $-(CH_2)_m-S$-alkyl, $-(CH_2)_m-S$-alkenyl, $-(CH_2)_m-S$-alkynyl, $-(CH_2)_m-S-(CH_2)_m-R_7$,



R_7 represents an aryl, a cycloalkyl, a cycloalkenyl, or a heterocycle;

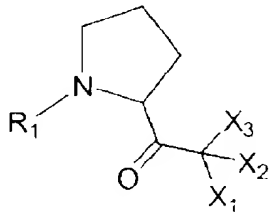
R_8 and R_9 each independently represent hydrogen, alkyl, alkenyl, $-(CH_2)_m-R_7$, -C(=O)-alkyl, -C(=O)-alkenyl, -C(=O)-alkynyl, or -C(=O)-$(CH_2)_m-R_7$,

or R_8 and R_9 taken together with the N atom to which they are attached complete a heterocyclic ring having from 4 to 8 atoms in the ring structure; ~~and~~

m is zero or an integer in the range of 1 to 8; and

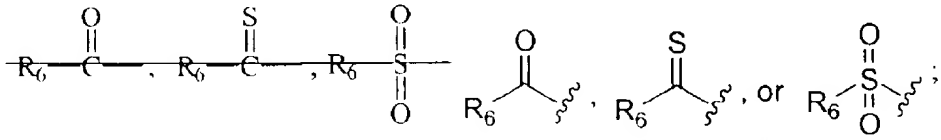
n is an integer in the range of 1 to 8.

27. 26. (Amended) The method of claim ~~14~~15, wherein the inhibitor is represented by the general formula:

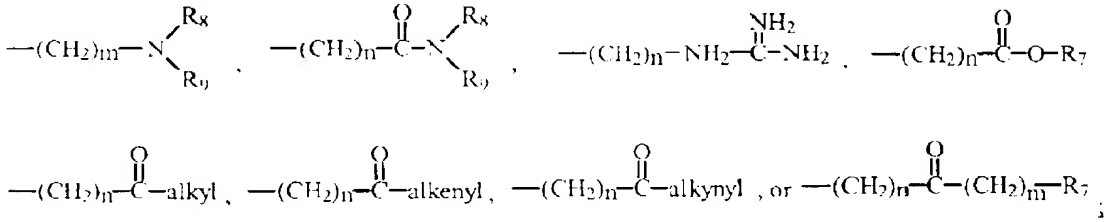


wherein ,

R_1 represents a C-terminally linked amino acid residue or amino acid analog, or a C-terminally linked peptide or peptide analog, ~~or~~



R_6 represents a hydrogen, a halogen, ~~a~~an alkyl, ~~a~~an alkenyl, ~~a~~an alkynyl, an aryl, -$(CH_2)_m$-R_7, -$(CH_2)_m$-OH, -$(CH_2)_m$-O-alkyl, -$(CH_2)_m$-O-alkenyl, -$(CH_2)_m$-O-alkynyl, -$(CH_2)_m$-O-$(CH_2)_m$-R_7, -$(CH_2)_m$-SH, -$(CH_2)_m$-S-alkyl, -$(CH_2)_m$-S-alkenyl, -$(CH_2)_m$-S-alkynyl, -$(CH_2)_m$-S-$(CH_2)_m$-R_7,



R_7 represents an aryl, a cycloalkyl, a cycloalkenyl, or a heterocycle;

R_8 and R_9 each independently represent hydrogen, alkyl, alkenyl, -$(CH_2)_m$-R_7, -C(=O)-alkyl, -C(=O)-alkenyl, -C(=O)-alkynyl, -C(=O)-$(CH_2)_m$-R_7,

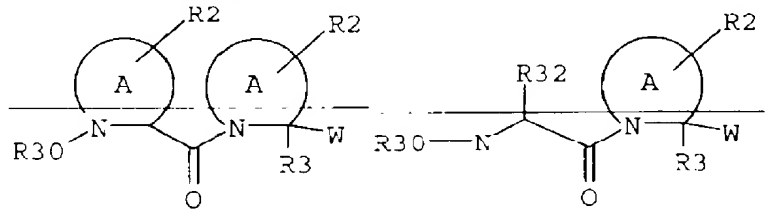
or R_8 and R_9 taken together with the N atom to which they are attached complete a heterocyclic ring having from 4 to 8 atoms in the ring structure;

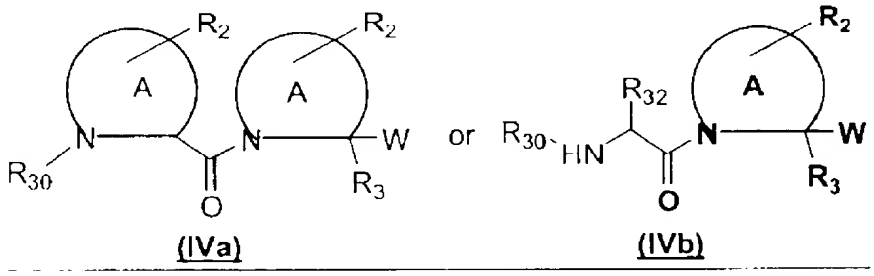
X_1, X_2 and X_3 each represent a hydrogen or a halogen; and

m is zero or an integer in the range of 1 to 8; and

n is an integer in the range of 1 to 8.

~~28~~. 27. (Amended) The method of claim ~~16~~15, wherein the inhibitor is represented by the general ~~formula~~ Formulae IVa or IVb:

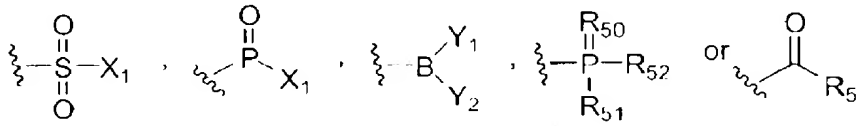




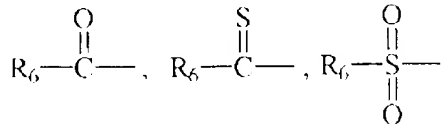
wherein,

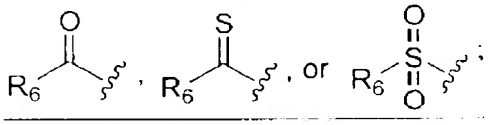
A represents a 4-8 membered heterocycle including a N and a Cα carbon;

W represents -CN, -CH=NR$_{52}$,



R_1 represents a C-terminally linked amino acid residue or amino acid analog, or a C-terminally linked peptide or peptide analog, or an amino-protecting group.

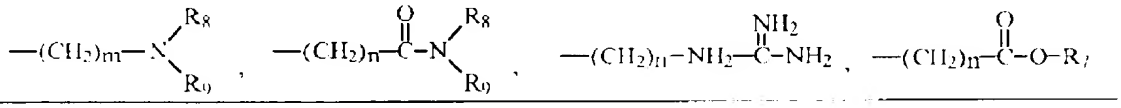


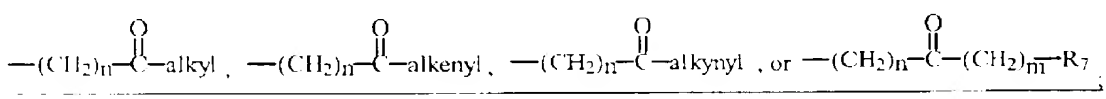


R_3 represents a hydrogen or a halogen, a lower alkyl, a lower alkenyl, a lower alkynyl, a carbonyl, an amino, an acylamino, an amido, a cyano, a nitro, an azido, a sulfate, a sulfonate, a sulfonamido, -$(CH_2)_m$-R_7, -$(CH_2)_m$-OH, -$(CH_2)_m$-O-lower alkyl, -$(CH_2)_m$-O-lower alkenyl, -$(CH_2)_n$-O-$(CH_2)_m$-R_7, -$(CH_2)_m$-SH, -$(CH_2)_m$-S-lower alkyl, -$(CH_2)_m$-S lower alkenyl, or -$(CH_2)_n$-S-$(CH_2)_m$-R_7;

R_5 represents a hydrogen, an alkyl, an alkenyl, an alkynyl, -$C(X_1)(X_2)X_3$, -$(CH_2)_m$-R_7, -$(CH_2)_n$-OH, -$(CH_2)_n$-O-alkyl, -$(CH_2)_n$-O-alkenyl, -$(CH_2)_n$-O-alkynyl, -$(CH_2)_n$-O-$(CH_2)_m$-R_7, -$(CH_2)_n$-SH, -$(CH_2)_n$-S-alkyl, -$(CH_2)_n$-S-alkenyl, -$(CH_2)_n$-S-alkynyl, -$(CH_2)_n$-S-$(CH_2)_m$-R_7, -C(O)C(O)NH_2, or -C(O)C(O)OR'$_7$;

R_6 represents a hydrogen, a halogen, an alkyl, an alkenyl, an alkynyl, an aryl, -$(CH_2)_m$-R_7, -$(CH_2)_m$-OH, -$(CH_2)_m$-O-alkyl, -$(CH_2)_m$-O-alkenyl, -$(CH_2)_m$-O-alkynyl, -$(CH_2)_m$-O-$(CH_2)_m$-R_7, -$(CH_2)_m$-SH, -$(CH_2)_m$-S-alkyl, -$(CH_2)_m$-S-alkenyl, -$(CH_2)_m$-S-alkynyl, -$(CH_2)_m$-S-$(CH_2)_m$-R_7,





R_7 represents, for each occurrence, a substituted or unsubstituted aryl, aralkyl, cycloalkyl, cycloalkenyl, or heterocyclyl;

R'$_7$ represents, for each occurrence, hydrogen, or a substituted or unsubstituted alkyl, alkenyl, aryl, aralkyl, cycloalkyl, cycloalkenyl, or heterocyclyl;

R_8 and R_9 each independently represent hydrogen, alkyl, alkenyl, $-(CH_2)_m-R_7$, -C(=O)-alkyl, -C(=O)-alkenyl, -C(=O)-alkynyl, or $-C(=O)-(CH_2)_m-R_7$,
or R_8 and R_9 taken together with the N atom to which they are attached complete a heterocyclic ring having from 4 to 8 atoms in the ring structure;
R_{30} is a small hydrophobic group; ~~and~~
R_{30} represents a C-terminally linked amino acid residue or amino acid analog, or a C-terminally linked peptide or peptide analog, or an amino-protecting group;

R_{50} represents O or S;

R_{51} represents N_3, SH, NH_2, NO_2 or OR'_7;

R_{52} represents hydrogen, a lower alkyl, an amine, OR'_7, or a pharmaceutically acceptable salt, or R_{51} and R_{52} taken together with the phosphorous atom to which they are attached complete a heterocyclic ring having from 5 to 8 atoms in the ring structure;

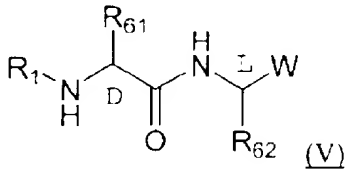
X_1 represents a hydrogen or a halogen, or a hydroxyl;

X_2 and X_3 each represent a hydrogen or a halogen;

m is zero or an integer in the range of 1 to 8; and

n is an integer in the range of 1 to 8.

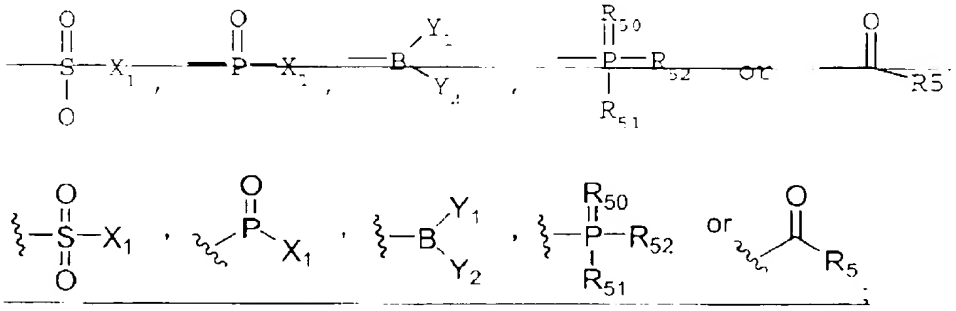
29. 28. (Amended) The method claim 16 1, 2, 3 ,4, or 15, wherein the inhibitor is represented by the general ~~formula~~ Formula V:



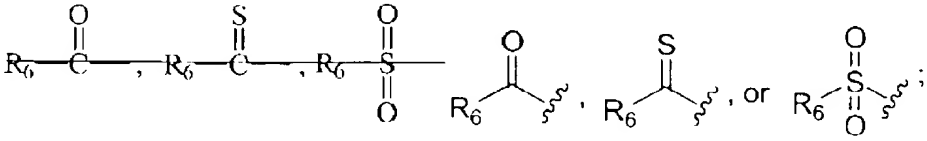
(V)

wherein,

W represents a functional group which reacts with an active site residue of the targeted protease as ~~for example,~~ selected from -CN, -CH NR_5,



R_1 represents a C-terminally linked amino acid residue or amino acid analog, or a C- terminally linked peptide or peptide analog, or an amino-protecting group, or



R_3 represents hydrogen or a halogen, a lower alkyl, a lower alkenyl, a lower alkynyl, a carbonyl ~~(such as a carboxyl, an ester, a formate, or a ketone)~~, a thiocarbonyl ~~(such as a thioester, a thioacetate, or a thioformate)~~, an amino, an acylamino, an amido, a cyano, a nitro, an azido, a sulfate, a sulfonate, a sulfonamido, - $(CH_2)_m$-R_7, -$(CH_2)_m$-OH, -$(CH_2)_m$-O-lower alkyl, -$(CH_2)_m$-O-lower alkenyl, -$(CH_2)_n$-O-$(CH_2)_m$-R_7, - $(CH_2)_m$-SH, -$(CH_2)_m$-S-lower alkyl, -$(CH_2)_m$-S-lower alkenyl, or - $(CH_2)_n$-S-$(CH_2)_m$-R_7;

R_5 represents H, an alkyl, an alkenyl, an alkynyl, -$C(X_1)(X_2)X_3$, -(CH_2)m-R_7, -(CH_2)n-OH, -(CH_2)n-O-alkyl, -(CH_2)n-O-alkenyl, -(CH_2)n-O-alkynyl, -(CH_2)n-O-(CH_2)m-R_7, -(CH_2)n-SH, -(CH_2)n-S-alkyl, -(CH_2)n-S-alkenyl, -(CH_2)n-S-alkynyl, -(CH_2)n-S-(CH_2)m-R_7, -C(O)C(O)NH_2, or -C(O)C(O)OR'$_7$;

R_6 represents a hydrogen, a halogen, aan alkyl, aan alkenyl, aan alkynyl, an aryl, -$(CH_2)_m$-R_7, -$(CH_2)_m$-OH, -$(CH_2)_m$-O-alkyl, -$(CH_2)_m$-O-alkenyl, -$(CH_2)_m$-O-alkynyl, -$(CH_2)_m$-O-$(CH_2)_m$-R_7, -$(CH_2)_m$-SH, -$(CH_2)_m$-S-alkyl, -$(CH_2)_m$-S-alkenyl, -$(CH_2)_m$-S-alkynyl, or -$(CH_2)_m$-S-$(CH_2)_m$-R_7;

R_7 represents, for each occurrence, a substituted or unsubstituted aryl, aralkyl, cycloalkyl, cycloalkenyl, or heterocycle;

R'_7 represents, for each occurrence, hydrogen, or a substituted or unsubstituted alkyl, alkenyl, aryl, aralkyl, cycloalkyl, cycloalkenyl, or heterocycle;

R_{61} and R_{62}, ~~independently~~independently, represent small hydrophobic groups;

Y_1 and Y_2 can independently or together be OH, or an alkoxyl, or ~~a group capable of being hydrolyzed to a hydroxyl group, including cyclic derivatives where~~taken together, Y1 and Y_2 are connected via a ring having from 5 to 8 atoms in the ring structure ~~(such as pinacol or the like),~~ which is hydrolyzed to hydroxy groups under physiological conditions;

R_{50} represents O or S;

R_{51} represents N_3, SH_2, NH_2, NO_2 or OR'_7;

R_{52} represents hydrogen, a lower alkyl, an amine, OR'_7, or a pharmaceutically acceptable salt, or R_{51} and R_{52} taken together with the phosphorous atom to which they are attached complete a heterocyclic ring having from 5 to 8 atoms in the ring structure;

X_1 represents a halogen;

X_2 and X_3, independently for each occurrence, represent a hydrogen or a halogen;

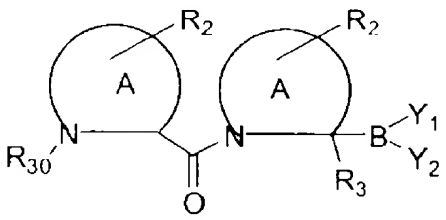
m is zero or an integer in the range of 1 to 8; and

n is an integer in the range of 1 to 8.

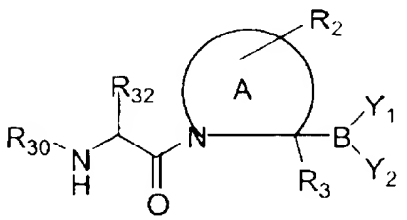
~~30.~~ 29. (Amended) A method for modfiying, in an animal, metabolism of peptide hormone, comprising administering to the animal a composition including one or more inhibitors of dipeptidylpeptidase IV (DPIV) with K_is of 1 nM or less ~~in an amount sufficient to increase the plasma half-life of a peptide hormone~~, which peptide hormone is selected from ~~the group consisting of~~ glucagon-like peptide 2 (GLP-2), growth hormone-releasing factor (GHRF), vasoactive intestinal peptide (VIP), peptide histidine isoleucine (PHI), pituitary adenylate cyclase activating peptide (PACAP), gastric inhibitory peptide (GIP), helodermin, Peptide YY and neuropeptide Y.

~~31.~~30. (Amended) A method for modifying glucose metabolism of an animal, comprising administering to the animal a composition including a boronyl peptidomimetic of a peptide selected from ~~the group~~ consisting Pro-Pro, Ala-Pro, and (D)-Ala-(L)-Ala.

~~32.~~31. (Amended) The method of claim ~~31~~30, ~~wherien~~wherein the boronyl peptidomimetic is represented in the general ~~formula:~~Formulae VIa-c,

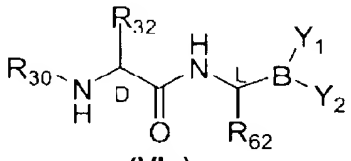


(VIa)



(VIb)

or



(VIc)

wherein,

each A independently represents a 4-8 membered heterocycle including ~~the~~a N and ~~the C~~ a Cα carbon;

R_2 is absent or represents one or more substitutions to the ring A, each of which can independently be a halogen, a lower alkyl, a lower alkenyl, a lower alkynyl, a carbonyl ~~(such as a carboxyl, an ester, a formate, or a ketone)~~, a thiocarbonyl ~~(such as a thioester, a thioacetate, or a thioformate)~~, an amino, an acylamino, an amido, a cyano, a nitro, an azido, a sulfate, a sulfonate, a sulfonamido, -$(CH_2)_m$-R_7, -$(CH_2)_m$-OH, -$(CH_2)_m$-O-lower alkyl, -$(CH_2)_m$-O-lower alkenyl, -$(CH_2)_n$-O-$(CH_2)_m$-R_7, -$(CH_2)_m$-SH, -$(CH_2)_m$-S-lower alkyl, -$(CH_2)_m$-S-lower alkenyl, or -$(CH_2)_n$-S-$(CH_2)_m$-R_7;

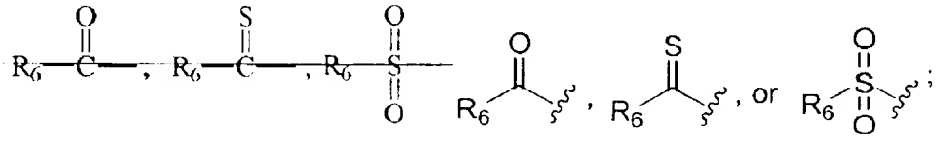
R_3 represents hydrogen or a halogen, a lower alkyl, a lower alkenyl, a lower alkynyl, a carbonyl ~~(such as a carboxyl, an ester, a formate, or a ketone)~~, a thiocarbonyl ~~(such as a thioester, a thioacetate, or a thioformate)~~, an amino, an acylamino, an amido, a cyano, a nitro, an azido, a sulfate, a sulfonate, a sulfonamido, - $(CH_2)_m$-R_7, -$(CH_2)_m$-OH, -$(CH_2)_m$-O-lower alkyl, -$(CH_2)_m$-O-lower alkenyl, -$(CH_2)_n$-O-$(CH_2)_m$-R_7, - $(CH_2)_m$-SH, -$(CH_2)_m$-S-lower alkyl, -$(CH_2)_m$-S-lower alkenyl, or - $(CH_2)_n$-S-$(CH_2)_m$-R_7;

~~R_5 represents H, an alkyl, an alkenyl, an alkynyl, $-C(X_1)(X_2)X_3$, $(CH_2)_m$-R_7, $(CH_2)_n$-OH, $(CH_2)_n$-O-alkyl, $(CH_2)_n$-O-alkenyl, $(CH_2)_n$-O-alkynyl, $(CH_2)_n$-O-$(CH_2)_m$-R_7, $(CH_2)_n$-SH, $(CH_2)_n$-S-alkyl, $(CH_2)_n$-S-alkenyl, $(CH_2)_n$-S-alkynyl, $(CH_2)_n$-S-$(CH_2)_m$-R_7, $-C(O)C(O)NH_2$, $-C(O)C(O)OR'_7$;~~

R_6 represents a hydrogen, a halogen, aan alkyl, aan alkenyl, aan alkynyl, an aryl, -$(CH_2)_m$-R_7, -$(CH_2)_m$-OH, -$(CH_2)_m$-O-alkyl, -$(CH_2)_m$-O-alkenyl, -$(CH_2)_m$-O-alkynyl, -$(CH_2)_m$-O-$(CH_2)_m$-R_7, -$(CH_2)_m$-SH, -$(CH_2)_m$-S-alkyl, -$(CH_2)_m$-S-alkenyl, -$(CH_2)_m$-S-alkynyl, or -$(CH_2)_m$-S-$(CH_2)_m$-R_7;

R_7 represents, for each occurrence, a substituted or unsubstituted aryl, aralkyl, cycloalkyl, cycloalkenyl, or heterocycle;

R_{30} represents a C-terminally linked amino acid residue or amino acid analog, or a C-terminally linked peptide or peptide analog, or an amino-protecting group, or



~~R_{32} and R_{61}, independently, represent small hydrophobic groups, preferably lower alkyls, and more preferably methyl~~;

R_{32} represents lower alkyl or halogen;

Y_1 and Y_2 can independently or together be OH, or and alkoxyl, or ~~a group capable of being hydrolyzed to a hydroxyl group, including cyclic derivatives where~~ taken together, Y_1 and Y_2 are connected via a ring having from 5 to 8 atoms in the ring structure ~~(such as pinacol or the like)~~, which is hydrolyzed to hydroxy groups under physiological conditions;

R_{62} represents lower alkyl or halogen;

m is zero or an integer in the range of 1 to 8; and

n is an integer in the range of 1 to 8.

33. 32. (Amended) The method of claim 32 31, wherein administering the boronyl peptidomimetic reduces one or more of insulin resistance, glucose intolerance, hyperglycemia, hyperinsulinemia, obesity, hyperlipidemia, or hyperlipoproteinemia.

34. 33. (Amended) The method of claim 32 31, wherein the boronyl peptidomimetic has an EC_{50} for modification of glucose metabolism which is at least one order of magnitude less than its EC_{50} for immunosuppression.

35. 34. (Amended) The method of claim 32 31, wherein the boronyl peptidomimetic has an EC_{50} for inhibition of glucose tolerance in the nanomolar or less range.

36. 35. (Amended) The method of claim 32 31, wherein the boronyl peptidomimetic has an EC_{50} for immunosuppression in the μM or greater range.

37. 36. (Amended) The method of claim 32 31, wherein the boronyl peptidomimetic is administered orally ~~active~~.

38. 37. (Amended) A method for modifying glucose metabolism of an animal, comprising administering to the animal a composition ~~including~~comprising a peptidomimetic boronyl inhibitor ~~of peptidomimetic of a~~wherein the peptide to be mimicked is selected from ~~the group consisting~~ Pro-Pro, Ala-Pro, and (D)-Ala-(L)-Ala.